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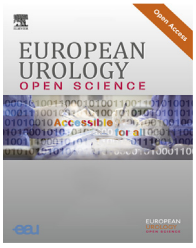

European Association of Urology

Open to Debate: For

Radiotherapy is the Preferred Primary Tumor Treatment in Oligometastatic Prostate Cancer

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Several retrospective studies based on the American Surveillance, Epidemiology and End Results database and the National Cancer Data Base have shown a survival benefit with local treatment in combination with androgen deprivation therapy (ADT) for men with de novo metastatic prostate cancer [1]. Whether this benefit is a true impact of the local treatment or because of imbalances between the treatment groups remains unanswered. Potential confounders besides missing information include age; comorbidity; performance status; secondary treatments; the site, number, and volume of metastases; initial and post-ADT prostate-specific antigen; Gleason score; and timing and dosages for the systemic treatment [1,2].

During the 2019 Advanced Prostate Cancer Consensus Conference, consensus was reached regarding the provision of local treatment with radiotherapy (RT) to the prostate for the majority of patients with newly diagnosed, low-volume, metastatic hormone-sensitive prostate cancer. Some 84% of the panelists voted for RT to the prostate and 16% voted for prostatectomy [3]. The question in the current debate is which is the optimal local therapy, RT or radical prostatectomy.

For RT, results from two prospective randomized trials have been published, HORRAD and Stampede arm H [4,5]. The HORRAD trial enrolled 432 patients with de novo metastatic prostate cancer to bone. Patients were randomized to ADT with or without RT to the prostate. For the whole cohort, overall survival (OS) did not significantly differ between the arms (median 45 vs 43 mo). However, there was a trend towards better OS for patients with five or fewer lesions treated with RT. In STAMPEDE arm H, 2061 patients with de novo metastatic prostate cancer were randomized to ADT with or without RT. No difference in the primary endpoint of OS at 3 yr was found (62% vs 65%). However, in the prespecified analysis of the patient group with low metastatic burden, RT improved 3-yr OS (81% vs 73%). A meta-analysis of both trials was performed by the STOPCAP M1 Radiotherapy Collaborators and showed a 7% improvement in 3-yr survival for men with fewer than five bone metastases [6]. In the HORRAD trial, local RT had relatively mild side effects and more urinary symptoms disappeared after 12 mo. For some patients (22%), bowel symptoms remained at 2 yr. The overall quality of life never deteriorated [7]. In addition, RT was well tolerated in the STAMPEDE trial, with 4–5% experiencing grade 3 or 4 adverse events during or after RT [5]. Altogether this resulted in a strong recommendation in the 2021 European Association of Urology guidelines on prostate cancer to offer ADT combined with prostate RT to patients whose first presentation is low-volume metastatic disease.

Data from the PEACE-1 trial (NCT01957436) will provide further information on the role of RT. PEACE-1 is a phase 3 trial with a 2 × 2 factorial design of abiraterone acetate plus

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prednisone and/or local RT for men with de novo metastatic hormone-sensitive prostate cancer. All patients receive continuous ADT as the standard of care (SOC) with or without docetaxel. Although first data from the PEACE-1 trial were presented at the 2021 American Society for Clinical Oncology and European Society for Medical Oncology meetings, no conclusions relevant to the current debate can be drawn yet.

To date, there are no mature data from phase 3 randomized trials available regarding the value of prostatectomy in de novo oligometastatic prostate cancer. Therefore, radical prostatectomy should not be offered outside a clinical trial. Theoretically, the morbidity associated with surgical treatment might have a negative effect on the immune system and on cancer control [8]. Results from the G-RAMMP, TRoMbone, and SWOG 1802 trials are eagerly awaited. In the G-RAMMP trial (NCT02454543), the effect of radical prostatectomy with extended lymphadenectomy in patients with limited bone metastatic prostate cancer is being evaluated. The TRoMbone trial (ISRTCN 15704862) is comparing radical prostatectomy including extended pelvic lymphadenectomy plus SOC to SOC alone, with SOC comprising ADT and other systemic therapies. The SWOG 1802 trial (NCT01751438) is an ongoing prospective randomized phase 2 trial comparing best systemic therapy with or without RT or surgery of the primary tumor in M1 prostate cancer.

Is there a mechanism of action that can explain the effect on distant lesions outside the RT treatment field the so-called abscopal effect? A possible explanation might be activation of the immune system. Multiple mechanisms of action of RT have been described, such as release of tumor antigens after damage to tumor cells, which leads to activation/maturation of dendritic cells and antigen-presenting cells, resulting in modulation of the tumor microenvironment [9]. Theoretically, addition of immunotherapy to local RT can further strengthen this effect to yield a therapeutically effective antitumor immune response, even in metastatic cancer [9].

Dudzinski et al. [10] used their syngeneic Myc-CaP murine model and established two tumors in each castrated FVB mouse of an experimental group. Anti–PD-1 or anti–PD-L1 antibodies were given and one tumor per mouse was irradiated with 20 Gy in two fractions. The nonirradiated tumor responded similarly to the irradiated tumor in the same mouse, which suggests the existence of an abscopal effect. A significant increase in median survival was found for mice treated with PD-1 or PD-L1 immune checkpoint inhibitors combined with RT when compared to drug therapy alone.

A proof of principle of the immunomodulatory effect of RT is the CA184-043 phase 3 trial, which evaluated RT to bone metastases (not the primary tumor) followed by ipilimumab (which binds to the inhibitory CTLA-4 and consequently enhances antitumor immunity) or placebo among 799 men with metastatic castrate-resistant prostate cancer who had received docetaxel. In the initial analysis, median OS was 11.2 mo with ipilimumab and 10.0 mo with placebo (hazard ratio 0.85, 95% confidence interval 0.72–1.00; p = 0.053). However, the preplanned long-term analysis revealed a significant OS advantage in the ipilimumab plus RT group [11].

In conclusion, when local treatment to the prostate is indicated in de novo oligometastatic prostate cancer, RT should be the treatment preferred over radical prostatectomy because of its proven effectiveness in randomized clinical trials, its low toxicity profile, and its potential immunomodulatory effects.

Conflicts of interest: The authors have nothing to disclose.

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